PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/57, 31/495 — A1

(11) International Publication Number: WO 96/15795

(43) International Publication Date: 30 May 1996 (30.05.96)

(21) International Application Number: PCT/US95/14938

(22) International Filing Date: 15 November 1995 (15.11.95)

(30) Priority Data:
08/341,651 17 November 1994 (17.11.94) US

(71) Applicant: UNIVERSITY OF SOUTHERN CALIFORNIA [US/US]; University Park Campus, Los Angeles, CA 90089 (US).

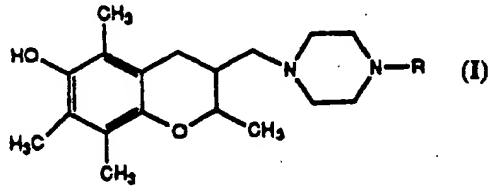
(72) Inventors: RODGERS, Kathleen, E.; 4403 Galeano Street, Long Beach, CA 90815 (US). diZEREGA, Gere, S.; 1270 Hillcrest Avenue, Pasadena, CA 91105 (US).

(74) Agent: MIAO, Emily; Banner & Allegretti, Ltd., Ten South Wacker Drive, Chicago, IL 60606 (US).

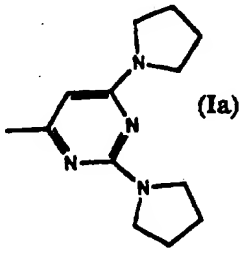
(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

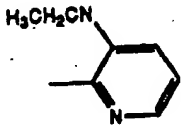
(54) Title: COMPOSITIONS CONTAINING LAZAROIDS AND THEIR USE FOR PREVENTING ADHESIONS



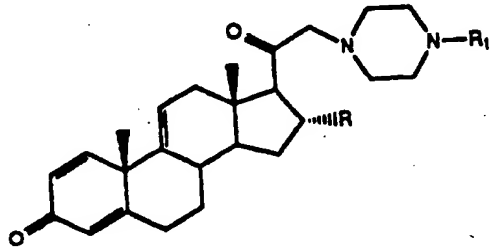
(I)



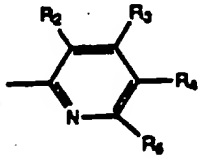
(Ia)



(Ib)



(II)



(IIa)

(57) Abstract

Compositions and method for the minimization or prevention of adhesion formation, whereby an effective amount of at least one lazaroid compound, preferably one of general formula (I), wherein R represents a formula (Ia) or (Ib), or formula (II), wherein R represents H or CH_3; R_1 represents formula (Ia) or formula (IIa), wherein R_2, R_3, R_4, and R_5 independently represent H or NR_6R_7, wherein R_6 and R_7 independently represent H and C_1-C_6 alkyl is administered for a period of time sufficient to permit tissue repair. The compound of general formulae (I) or (II) is preferably administered in conjunction with a delivery vehicle (e.g., microcapsules, microspheres, biodegradable polymer films, lipid-based delivery systems such as liposomes and lipid foams, viscous instillates and absorbable mechanical barriers) useful for maintaining local concentrations of the compound at an effective level.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

COMPOSITIONS CONTAINING LAZAROIDS AND THEIR USE FOR PREVENTING ADHESIONS

FIELD OF THE INVENTION

The present invention relates to compositions comprising lazaroids thereof and their use in a method for preventing post-operative adhesion formation between organ surfaces.

BACKGROUND OF THE INVENTION

Adhesion formation, in particular following peritoneal surgery, is a major source of postoperative morbidity and mortality. Appendectomy and gynecologic surgery are the most frequent surgical procedures implicated in clinically significant adhesion formation. The most serious complication of intraperitoneal adhesions is intestinal obstruction; in addition, adhesions are associated with chronic or recurrent pelvic pain and infertility in females.

The pathogenesis of adhesion formation is complex and not entirely understood. The first step is believed to involve excess fibrin deposition to form a scaffold. Organization of the fibrin scaffold by cellular elements, including fibroblasts and mesothelial cells, then follows.

Various approaches for the prevention of adhesion formation have been actively explored [diZerega, G.S. & Rodgers, K.E., "Prevention of Postoperative Adhesions," in "The Peritoneum," diZerega, G.S. & Rodgers, K.E., eds., Springer-Verlag, New York, pp. 307-369 (1992)]. In general, the treatments fall into three categories: prevention of fibrin deposition in the peritoneal exudate, reduction of local tissue inflammation; and removal of fibrin deposits.

Therapeutic attempts to prevent fibrin deposition include peritoneal lavages to dilute or wash away fibrinous exudate, surgical techniques to minimize tissue ischemia and introduction of barriers to limit apposition of healing serosal surfaces. Although the use of agents affecting coagulation of the fibrinous fluid has also been proposed, results obtained to date suggest that the use of procoagulants in areas of substantial bleeding may actually promote adhesion formation [Elkins, T.E., "Can a Pro-Coagulant Substance Prevent Adhesions?" in "Treatment of Post-Surgical Adhesions," diZerega, G.S. et al., eds., Wiley-Liss, New York, pp. 103-112 (1990)].

Physical barriers have been used in attempts to prevent adhesion formation by limiting tissue apposition during the critical period of peritoneal healing, thereby minimizing the development of fibrin matrix between tissue surfaces. Barrier agents which have been employed include both mechanical barriers and viscous solutions. Mixed results have been obtained using a barrier comprising a thin sheet of expanded poly-tetrafluoroethylene; in any event, such a membrane is less than ideal, as it must be sutured into place and is nonabsorbable. While an absorbable barrier (for example, a barrier made of oxidized regenerated cellulose) would be preferable, not all studies have demonstrated the efficacy of such barriers in preventing adhesions. Liquid barriers have also been considered for use in preventing adhesions; for example, chondroitin sulfate and carboxymethyl cellulose have both shown some promise in animal models. In addition, solution of dextran 70 (molecular weight = 70,000) have been the subject of a number of clinical studies. Not all clinical evaluations of 32% dextran 70 have found a therapeutic effect, however, and the clinical use of the solution is also associated with clinically important side effects.

Anti-inflammatory drugs have been evaluated for their effects on postoperative adhesion formation, as they may limit the release of fibrinous exudate in response to inflammation at the surgical site. Two general classes of these drugs were tested: cortico-steroids and nonsteroidal anti-inflammatory drugs. The results of corticosteroid use in animal studies have generally not been encouraging, and clinical use of corticosteroids is limited by their other pharmacologic properties. While experimental evaluations of nonsteroidal anti-inflammatory drugs in postoperative adhesion formation show promise [Rodgers, K.E., "Nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of Postsurgical adhesion," in "Treatment of Post-Surgical Adhesions," diZerega, G.S. et al., eds., Wiley-Liss, New York, pp. 119-129 (1990)], clinical evaluations of these drugs for adhesion prevention is needed.

The third approach explored to date involves the removal of fibrin deposits. Although proteolytic enzymes (e.g., pepsin, trypsin and papain) should theoretically augment the local fibrinolytic system and limit adhesion formation, these enzymes are rapidly neutralized by peritoneal exudates rendering them virtually useless for adhesion prophylaxis. While various fibrinolytics (for example, fibrinolysin, streptokinase and urokinase) have been advocated, a potential complication to the clinical use of these enzymes in postoperative therapy is excessive bleeding resulting from their administration. Topical application of a recombinant tissue plasminogen activator (rt-PA) has been shown to reduce adhesion formation in a variety of animal models; further research is necessary to develop suitable delivery systems to provide this drug to the surgical site and identify the postoperative time when adhesion prevention is feasible.

To date, no single therapeutic approach has proven universally effective in preventing formation of postoperative intraperitoneal adhesions. Therefore, there is a need for compositions and methods which may be used safely and effectively to prevent adhesion formation in a variety of different contexts.

Objects of the Invention

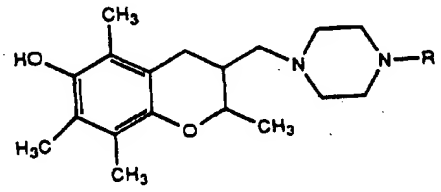
It is an object of the present invention to provide lazaroid-based compositions for use in preventing or minimizing adhesion formation.

It is another object of the invention to provide methods for the minimization or prevention of post-surgical adhesion formation employing compositions.

These and other objects of the invention will be apparent in light of the detailed description below.

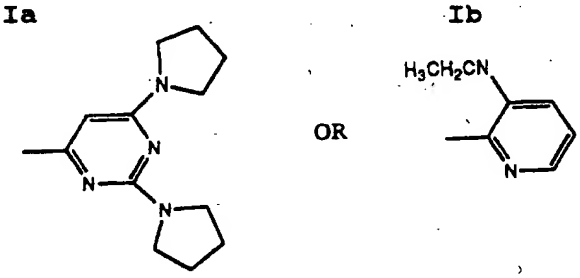
Summary of the Invention

The present invention relates to a method for the minimization or prevention of adhesion formation comprising administering to a subject an effective amount of a composition comprising at least lazaroid compound to effect tissue repair. Preferably, the composition includes at least one lazaroid compound of the general formula I:

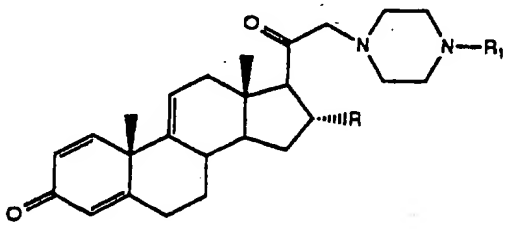


wherein R represents a formula:

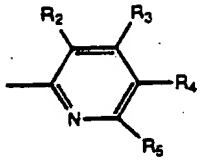
Ia Ib



or formula II:



wherein R represents H or CH_3; R_1 represents formula Ia, as defined above, or formula IIa:



wherein R_2, R_3, R_4, and R_5 independently represent H or NR_6R_7 wherein R_6 and R_7 independently represent H and C_1-C_6 alkyl. The composition also includes a drug delivery system which maintains an effective concentration of the compound at a site of potential adhesion formation during the perioperative interval.

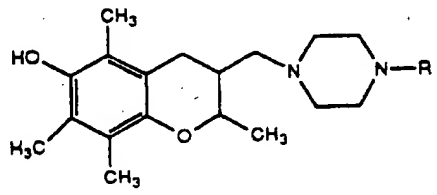
Pursuant to another aspect of the present invention, adhesion formation is minimized or prevented by administration of at least one lazaroid compound, preferably one of the general formulae I or II, at a site of potential adhesion formation for a period of time sufficient to permit substantial tissue repair (e.g., re-epithelialization or mesothelial repair) at the site.

DETAILED DESCRIPTION OF THE INVENTION

All literature references, patents and patent applications cited in this application are incorporated herein in their entirety.

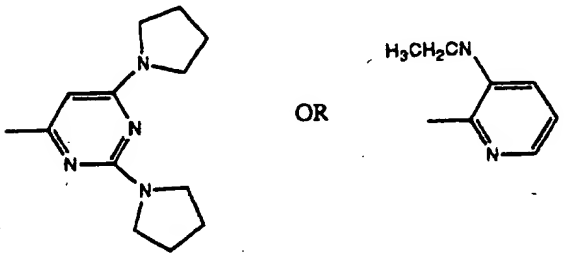
The inventive composition and method are useful in minimizing or preventing formation of adhesions between organ surfaces (not cell-to-cell adhesion), the most common cause of which is prior surgery. The inventive composition and method have been shown to be especially effective in preventing adhesion formation in the peritoneum following surgery. In addition, the present invention finds utility in other contexts, e.g., for cardiovascular, orthopedic, thoracic, ophthalmic, CNS and other uses, where prevention of the formation of adhesions is a significant concern. For example, prevention of adhesion formation or drug loculation during the intraperitoneal administration of chemotherapeutic agent is contemplated as within the scope of the present invention. For the purposes of the following discussion, attention is directed primarily to description of compositions and methods useful in inhibiting peritoneal adhesion formation.

The present invention contemplates the use of a composition comprising at least one lazaroid compound. Suitable, but non-limiting, examples of lazaroids and their preparation for use in the invention include, for instance, the aminosteroids represented in WO 87/01706. Preferably, the composition includes at least one lazaroid compound of the general formula I:

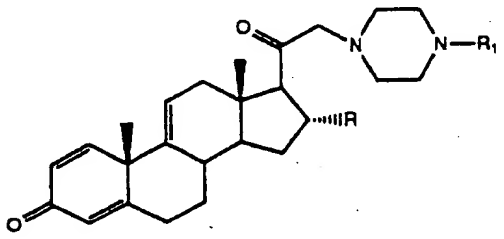


wherein R represents a formula:

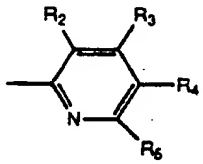
Ia Ib



or formula II:



wherein R represents H or CH_3; R_1 represents formula Ia, as defined above, or formula IIa:



wherein R_2, R_3, R_4, and R_5 independently represent H or NR_6R_7 wherein R_6 and R_7 independently represent H and C_1-C_6 alkyl. The lazaroids are preferably used in a form of a pharmaceutically acceptable salt, hydrate or solvate such as the ones described in WO 87/01706 and U.S. Patent No. 5,256,408.

A particularly preferred Formula I lazaroids for use in the invention are **U83,836E** ((-)-2-[[4-(2,6-Di-1-pyrrolindinyl-4-pyrimidinyl)-1-piperazinyl] methyl]-3,4-dihydro-2,5,7,8-tetramethyl-2H-1-benzopyran-6-ol, dihydrochloride); **U-78517G** (same as U-83836E except 2-hydroxy-1,2,3-propanetricarboxylate (1:2) salt form is

used); **U-78518E** (2H-1-benzopyran-6-ol,2-[[4-[3-(ethylamino)-2-pyridinyl]-1-piperazinyl]methyl]-3,4-dihydro-2,5,7,8-tetramethyl-, hydrochloride); **U-78517F** (a racemic mixture of U-83,836 and its enantiomer); and **U-78518F** (same as U-78518E except that the (Z)-2-butenedioate salt form is used), all produced by the UpJohn Company (Kalamazoo, Michigan, USA).

Preferred formula II lazaroid compounds for use in the invention include **U-74500A** (pregna-1,4,9(11)-triene-3,20-dione, 21-[4-[5,6-bis(diethylamino)-2-pyridinyl]-1-piperazinyl]-16-methyl-, hydrochloride, (16.alpha.)-); **U-75412E** (21-[4-[3-ethylamino)-2-pyridinyl]-1-piperazinyl-16-methyl-pregna-1,4,9(11)-trien-3,20-dione,(16.alpha.)-(Z)-2-butenedioate (1:1)); **U-75412A** (same as U-75412E except the hydrochloride form is used); **U-74006F** (21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16-methyl-16.alpha.)-pregna-1,4,9(11)-triene-3,20-dione monomethanesulfonate; also known as tirilazad mesylate); **U-74389G** (21-(4-(2,6-di-1-pyrrolindinyl-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione, (Z)-2-butenedioate (1:1)); **U-74389F** (same as U-74389G except that the monomethanesulfonate salt form is used); **U-77372E** (16-alpha-methyl-21-[4-[4,6-bis(2-pyridinyl)-1,3,5-triazin-2-yl]-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione, monomethanesulfonate); and **U-78000E** (16-alpha-methyl-21-[4-[2,6-bis(2-pyridinyl)-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione, monomethanesulfonate), all produced by the UpJohn Company (Kalamazoo, Michigan, USA). These aminosteroids and methods for their preparation is described in WO 87/01706, published March 26, 1987.

Other useful 21-aminosteroid lazaroids such as **U-74915**, **U-75014E**, and **U-75013E** and their syntheses are reported in J.M. Braughler et al. "Novel Membrane Localized Iron Chelators as Inhibitors of Iron-dependent Lipid Peroxidation," Biochem. Pharm., Vol. 37, pp. 3853-60

(1988).

In addition, U-79206 (Ethanol, 2-[(2,6-di-1-pyrrolidinyl)-4-pyrimidinylmethylamino]) and U-76556 (4-[3-(ethylamino)-2-pyridinyl] piperazine), also produced by the UpJohn Company (Kalamazoo, Michigan, USA), are also preferred in practicing the invention.

Lazaroids are a unique group of 21-aminosteroids and 2-methylaminochromans compounds which exert a protective effect against tissue damage after trauma and/or ischemia. See, e.g., P.D. Thomas et al. (1993) "Inhibition of Superoxide-generating NADPH Oxidase of Human Neutrophils by Lazaroids (21-aminosteroids and 2-methylaminochromans)," Biochem. Pharmacol., Vol. 45, pp. 241-251); E.D. Hall (1992) "Novel Inhibitors of Iron-dependent Lipid Peroxidation for Neurodegenerative Disorders," Ann. Neuro., Vol. 32 (Suppl.), pp. 137-42. In several animal models of traumatic and ischemic injury to the central nervous system, lazaroids have been shown to prevent secondary tissue injury associated with oxidative cell damage. E.D. Hall et al. (1992), ibid.

The protective effects of lazaroids have been attributed to their ability to inhibit lipid peroxidation reactions as well as reduce production of reactive oxygen metabolites (e.g., hydrogen peroxide and free radicals) by leukocytes and monocytes. See, e.g., J.M. Braughler et al. "Novel 21-Amino Steroids as Potent Inhibitors of Iron-dependent Lipid Peroxidation," J. Biol. Chem., Vol. 262(22), pp. 10438-10440 (1987)). Lazaroids have been shown to inhibit the respiratory burst of neutrophils and monocytes. See, e.g., S.M. Shappell et al. "Inhibition of Neutrophil Beta-2-Integrin-mediated H_2O_2 production by Lazaroids U75412 and U78517," FASEB J. A1428; Fisher et al. "A 21-aminosteroid Inhibits Stimulated Monocyte Hydrogen Peroxide and Chemiluminescence Measurements form MS patients and Controls," Neurology, Vol. 41, pp 297-299

(1991); Fisher et al. "A 21-Aminosteroid Reduces Hydrogen Peroxide Generation by and Chemiluminescence of Stimulated Human Leukocytes," Stroke, Vol. 21, pp 1435-1438 (1990); P.D. Thomas et al, Ibid).

Lazaroids and related compounds where also found to inhibit cell proliferation in vitro. See, e.g., R.S. Kim et al. "Antiproliferative Properties of Aminosteroid Antioxidants on Cultured Cancer Cells," Cancer Letters, Vol. 64(1), pp 61-66 (1992); J.P. Singh et al. "Inhibition of Proliferation of Fibroblasts by Lazaroids (21-Aminosteroids)," Life Sciences, Vol. 49, pp. 2053-2058 (1991). However, a comparison of various lazaroids and other known antioxidants with similar antioxidant potential, e.g. vitamin E and Probucol, suggested that cell growth inhibition by lazaroids may be unrelated to their antioxidant activity. J.P. Singh et al. (1991), ibid.

While the present invention is not bound to any particular theory, it is believed that lazaroid compounds such as those of general formulae I and II (and in particular, U83,836e) may inhibit adhesion formation through a variety of mechanisms. For instance, reduction of lipid peroxidation after ischemia is thought to increase the fibrinolytic potential of the peritoneum and this may account for diminished adhesion formation. In addition, release of arachidonic acid from cells is blocked by these compounds due to membrane stabilizing effects, not inhibition of phospholipase A_2. See, e.g., J.M. Braughler et al. "The 21-aminosteroid Inhibitors of Lipid Peroxidation Reactions with Lipid Peroxyl and Phenoxyl Radicals," Free Rad. Biol. & Med., Vol. 7, pp. 125-139 (1989); J.M. Braughler et al. "Central Nervous System Trauma and Stroke. I. Biochemical Considerations for Oxygen Radical Formation and Lipid Peroxidation," Free Rad. Biol. & Med., Vol. 6, pp. 289-301 (1989); J.M. Braughler et al. "Novel Membrane Localized Iron Chelators as Inhibitors of

Iron-dependent Lipid Peroxidation," Biochem. Pharm., Vol. 37, pp. 3853-60 (1988); N. Aoki et al. "Protective Effects of a Novel Non-glucocorticoid 21-Aminosteroid (U74006F) during traumatic Shock in Rats," J. Cardiovas. Pharm., Vol. 15, pp. 205-210 (1990); E.D. Hall et al. "Nonsteroidal Lazaroid U78517F in Models of Focal and Global Ischemia," Stroke, Vol. 21, III-83-7 (1990); M. Choi et al. "U75412E, a Lazaroid, Prevents Progressive Burn Ischemia in a Rat Burn Model," Amer. J. Path., Vol. 142, pp. 519-528 (1993).

As is well recognized in the art, however, no one of these possible mechanisms of action of lazaroids, e.g., U83,836e and other compounds of general formulae I and II, would in and of itself be sufficient to enable one to predict whether these compounds would have any utility in reduction of adhesion formation.

For example, lazaroids inhibit the respiratory burst of neutrophils and monocytes. S.M. Shappell, "Inhibition of Neutrophil Beta-2-Integrin-mediated H_2O_2 Production by Lazaroids U75412 and U78517," FASEB J., A1428; M. Fisher et al. (1991), supra; M. Fisher et al. (1990), supra; P.D. Thomas et al. (1993), supra. In contrast, tolmetin, a NSAID agent also shown to reduce adhesion formation, has been shown to increase the production of oxygen radicals by postoperative macrophages in rabbits (K. Rodgers et al. (1988) "Effects of tolmetin sodium dihydrate on normal and post-surgical peritoneal cell function," Int'l. J. Immunopharm., Vol 10, pp. 111-120)). Moreover, lazaroids inhibit cellular proliferation which is believed to be necessary for re-epithelialization of the injured site and for prevention of adhesions. See, e.g., R.S. Kim et al. (1992), supra, and J.P. Singh et al (1991), supra.

Pursuant to the method of the present invention, at least one lazaroid compound, preferably one of general formulae I or II, is maintained in an effective concentration at the site of potential adhesion formation

for a period of time sufficient to permit substantial re-epithelialization. The lazaroid compound is typically administered over the perioperative interval, which for purposes of the present invention may include time shortly prior to surgery through the surgery itself up to some time after completion of surgery. The term of administration may vary depending upon a number of factors which would be readily appreciated those skilled in the art. In general, administration of a composition in accordance with the present invention including at least one lazaroid compound should be effected from the time of surgery for at least 24 to 48 hours after completion of the surgical procedure. As healing is in most cases complete within about two weeks, it is generally not necessary to continue administration of a composition in accordance with the present invention much longer than two weeks. The composition in accordance with the present invention comprising at least one lazaroid compound is administered from about the time of surgery for a period ranging between about 24 hours and about 14 days, preferably ranging between about 24 hours and about 7 days and most preferably ranging between about 24 and about 72 hours.

The rate of administration of the lazaroid compound may be varied over a fairly broad range. The concentrations of the lazaroid compound I which can be administered would be limited by efficacy at the lower end and the solubility of the compound at the upper end. With respect to compositions comprising lazaroids, the concentration ranges are as follows:

General Range	Preferred Range
0.04 ng-0.2mg/hr/kg	0.04-40μg/hr/kg
0.007ng-0.033mg /hr/cm^2	0.007-6.7μg /hr/cm^2
0.0027ng-0.013mg /hr/cm^2/kg	0.0027-2.67μg/ hr/cm^2/kg

As defined herein, kg refers to body weight of the subject and cm^2 refers to the surface area of the injury site to be treated. The wt/hr/cm^2 ranges are generally used for intercavitary administration of lazaroid compounds with liquid or barrier delivery systems.

The lazaroid compound may be administered directly in a suitable vehicle, e.g., a solution of citric acid, sodium citrate and sodium chloride, to a site at which it is desired to prevent adhesion formation. For example, U.S. Patent Nos. 5,256,408 and 4,968,675 which describe examples of suitable vehicles for aminosteriod lazaroids for topical ophthalmic and parenteral use, respectively. Pursuant to preferred embodiments of the present invention, however, at least one lazaroid compound is administered in a single dose delivery (for example, prior to suturing after surgery) using a drug-delivery system which enables the maintenance of requisite concentrations of the compound for a period of time sufficient for re-epithelialization. A suitable drug-delivery system would itself be essentially inactive (i.e., essentially non-inflammatory and non-immunogenic) and would permit release of the lazaroid compound so as to maintain effective levels thereof over the desired time period.

A large variety of alternatives are known in the art as suitable for purposes of sustained release and are contemplated as within the scope of the present invention. Suitable delivery vehicles include, but are not limited to, the following: microcapsules or microspheres; liposomes and

other lipid-based release systems; viscous instillates; absorbable and/or biodegradable mechanical barriers; and polymeric delivery materials, such as polyethylene oxide/polypropylene oxide block copolymers (e.g. poloxamers), poly-orthoesters, cross-linked polyvinyl alcohol, polyanhydrides, polymethacrylate and polymethacryladmide hydrogels, anionic carbohydrate polymers, etc.. Useful delivery systems are well known in the art and are described in, e.g., U.S. Patent No. 4,937,254, the entire disclosure of which is hereby incorporated by reference.

One particularly suitable formulation to achieve the desired near zero-order release of at least one lazaroid compounds such as the compounds of general formulae I or II comprise injectable microcapsules or microspheres prepared from a biodegradable polymer, such as poly(dl-lactide), poly(dl-lactide-co-glycolide), poly-caprolactone, polyglycolide, polylactic acid-co-glycolide, poly(hydroxybutyric acid), a polyortho-ester or a polyacetal. Injectable systems comprising microcapsules or microspheres of a diameter on the order of about 50 to about 500 μm offer advantages over other delivery systems. For example, they generally use less active agent and may be administered by paramedical personnel. Moreover, such systems are inherently flexible in the design of the duration and rate of separate drug release by selection of microcapsule size, drug loading and dosage administered. In addition, such microcapsules can be successfully sterilized with gamma irradiation.

Microcapsules are systems comprising a polymeric wall that encloses a liquid or solid core. The capsule wall usually does not react with the core material; however, it is designed to provide sufficient strength to enable normal handling without rupture while being sufficiently thin to allow a high core to wall volume ratio. The capsule

contents remain within the wall until released by diffusion or other means that dissolve, melt, break, rupture or remove the capsule material. Preferably, the capsule wall can be made to degrade and decompose in suitable environments while diffusing the core material through the capsule wall to allow for its slow, prolonged delivery.

The mechanism of release in biodegradable microcapsules is a combination of drug diffusion and polymer biodegradation. Therefore, the rate and duration of release are determined by microcapsule size, drug content and quality, and polymer parameters such as crystallinity, molecular weight and composition. In particular, adjustment in the amount of drug released is generally achieved by modification of capsule wall thickness, capsule diameter, or both. Detailed information concerning the design, preparation and use of microspheres and microcapsules is provided by, e.g., Lewis, D.H., "Controlled Release of Bioactive Agents from Lactide/Glycolide Polymers," in "Biodegradable Polymers as Drug Delivery Systems," Jason & Langer, eds., pp. 1-41 (1990), the entire disclosure of which is hereby incorporated by reference. The sustained intraperitoneal release of dexamethasone using poly(lactide-co-glycolide) microparticles is described in Hoeckel, M. et al., "Prevention of Peritoneal Adhesions in the Rat with Sustained Intraperitoneal Dexamethasone Delivered by a Novel Therapeutic System," Annales Chirurgiae et Gynaecologiae, Vol. 76, pp. 306-313 (1987), the entire disclosure of which is also incorporated by reference.

As is well known to those skilled in the art, various methods are currently available for preparing microcapsules, any of which could be employed to provide formulations in accordance with the present invention. Biodegradable polymeric materials suitable for preparation of microcapsules for controlled (i.e., near zero-order)

release would be readily determined through routine experimentation by those skilled in the art. Moreover, alternative delivery systems suitable for use in accordance with the present invention (for example, fibers or filaments comprising the active agents) based on biodegradable polymers are also contemplated as within the scope of the present invention.

An alternative approach for the single-dose delivery of at least one lazaroid compound involves the use of biodegradable polymers, such as the ones described above, in the form of a film. Such films may be produced by spraying or discharging dispersed liquid droplets containing the biopolymer and at least one lazaroid in a suitable carrier from a pressurized container onto the targeted site.

Another approach for the single-dose delivery of at least one lazaroid compound, in accordance with the present invention, involves the use of liposomes and other lipid-based delivery systems. The encapsulation of an active agent in multilamellar vesicles (or liposomes) is a well known technique to assist in target drug delivery and prolong drug residence. In a typical procedure, a liposome-forming powdered lipid mixture is added to the desired quantity of active agent in aqueous solution (e.g., phosphate buffered saline) to form a suspension. After a suitable hydration period, the hydrated suspension is then autoclaved to provide the liposome-active agent preparations. A lipid mixture suitable for formation of liposomes may be prepared from L-alpha-distearoyl phosphatidylcholine and cholesterol dissolved in chloroform, to which alpha-tocopherol is added; other compositions and methods for formation of liposomes would, however, also be useful for this purpose. The intraperitoneal administration of liposomes containing ibuprofen or tolmetin is described in Rodgers, K. et al.,

"Inhibition of Postsurgical Adhesions by Liposomes Containing Nonsteroidal Anti-inflammatory Drugs," Int. J. Fertil., Vol. 35, p. 40 (1990), the entire disclosure of which is hereby incorporated by reference.

Other lipid-based delivery systems are also contemplated for use in this invention. One useful system includes lipid foams such as DepoFoam extended-release formulations comprising spherical particles bounded by a single bilayer lipid membrane and each containing numerous nonconcentric aqueous chambers which encapsulate the active ingredient (see, e.g, Kim, T.K. et al. (1993) "Extended-release formulation of morphine for subcutaneous administration," Cancer Chemother. Pharmacol., Vol. 33, 187; Chatelut, E. et al. (1993) "A slow-release methotrexate formulation for intrathecal chemotherapy," Cancer Chemother. Pharmacol., Vol. 32, 179.] Such lipid particles are made from nontoxic lipids identical to those found in cell membranes.

Yet another suitable approach for single dose delivery of at least one lazaroid compound, in accordance with the present invention involves the use of so-called viscous instillates. In this technique, high-molecular-weight carriers are used in admixture with the active agents, giving rise to an extended structure include, but are not limited to, the following: dextrans and cyclodextrans; hydrogels; cross-linked viscous materials, including viscoelastics and cross-linked viscoelastics; carboxymethylcellulose; and hyaluronic acid. While some studies have suggested that the use of viscous barrier solutions per se may have an advantageous effect in reducing the incidence of adhesion formation, it is believed that any such effect is of limited scope when compared to the combination of at least one lazaroid compound and carrier. The intraperitoneal administration

of a viscous instillate comprising tolmetin is described in Abe, H. et al., "The Effect of intra-peritoneal Administration of Sodium Tolmetin-Hyaluronic Acid on the Postsurgical Cell Infiltration *In Vivo*," J Surg. Res., Vol. 49, p. 322 (1990), the entire disclosure of which is hereby incorporated by reference.

Pursuant to yet another approach, the lazaroid compound is administered in combination with an absorbable mechanical barrier which alone reduces adhesion formation. As would be readily apparent to one working in the field, a lazaroid compound, preferably one of general formulae I or II, may be covalently or non-covalently (e.g., ionically) bound to such a barrier, or it may simply be dispersed therein. A particularly suitable mechanical barrier for use in this particular embodiment of the invention comprises oxidized regenerated cellulose; one such absorbable barrier is available under the designation INTERCEED(TC7) from Johnson and Johnson Medical, Inc., New Brunswick, New Jersey [INTERCEED(TC7) Adhesion Barrier Study Group, "Prevention of postsurgical adhesions by INTERCEED(TC7), an absorbable adhesion barrier: a prospective, randomized multicenter clinical study," Fertility and Sterility, Vol. 51, p. 933 (1989)]. The use of a mechanical barrier as a carrier to deliver heparin to traumatized surfaces is disclosed in Diamond, M. P. et al., "Synergistic effects of INTERCEED(TC7) and heparin in reducing adhesion formation in the rabbit uterine horn model," Fertility and Sterility, Vol. 55, p. 389 (1991) and Diamond, M.P. et al., "Adhesion reformation: reduction by the use of INTERCEED(TC7) plus heparin," J. Gyn. Surg., Vol. 7, p. 1 (1991), the entire disclosures of which are hereby incorporated by reference.

The invention may be better understood with reference to the accompanying examples, which are intended to be illustrative only and should not be viewed as in any sense

limiting the scope of the invention, which is defined hereinafter in the accompanying claims.

Examples

Multiple studies to confirm the efficacy of a lazaroid compound, exemplary compound U83,836e, in the reduction of adhesion formation after peritoneal surgery were performed. Two model systems were employed: the sidewall adhesion model and the uterine horn model. A clear correlation between results obtained using both of these models and utility in adhesion prevention has been demonstrated with INTERCEED(TC7), for which clear clinical efficacy has been shown and FDA approval for adhesion prevention in gynecological surgery has been obtained.

In the peritoneal sidewall model, rabbit were pre-anesthetized with 1.2 mg/kg acetylpromazine and anesthetized with a mixture of 55 mg/kg ketamine hydrochloride and 5 mg/kg xylazine intramuscularly. Following preparation for sterile surgery, a midline laparotomy was performed. A 3 x 5-cm area of peritoneum and transversus abdominis muscle was removed on the right lateral abdominal wall. The cecum was exteriorized, and digital pressure was exerted to create subserosal hemorrhages over all cecal surfaces. The cecum was then returned to its normal anatomic position. The compound to be tested was placed in an Alzet minoosmotic pump (Alza Corporation, Palo Alto, CA, USA) to allow continuous release of the molecule through the postsurgical interval. The Alzet miniosmotic pump was placed in the subcutaneous space and a delivery tube connected the pump with the site of injury at sidewall. Vehicle was placed in the pump of control rabbits. The abdominal wall and skin were closed in a standardized manner.

After 7 days, the rabbits were sacrificed and the percentage of the area of the sidewall injury that is

involved in adhesions was determined. In addition, the tenacity of the adhesion formed was scored use a system as follows:

0	=	No adhesions
1	=	mild, easily dissectable adhesions
2	=	moderate adhesions; non-dissectable, does not tear organ
3	=	dense adhesions; non-dissectable, tears when removed

A reduction in the area or the tenacity of the adhesions would be considered beneficial.

In additional experiments, a rabbit uterine horn model was employed. This model has been previously shown to cause severe adhesions in rabbits after surgery [Nishimura, K. et al., "The Use of Ibuprofen for the Prevention of Postoperative Adhesions in Rabbits," Am. J. Med., Vol. 77, pp. 102-106 (1984)]. The rabbits were anesthetized (130 mg/kg ketamine and 20 mg/kg acetylpromazine im) and prepared for sterile surgery. A midline laparotomy was performed, and surgical trauma was performed on both uterine horns by abrading the serosal surface with gauze until punctate bleeding developed. Ischemia of both uterine horns was induced by removal of the collateral blood supply. After traumatization, the abdominal wall was closed in two layers. The compound to be tested was delivered as described for the peritoneal sidewall model, but the tubing was placed over the injured uterine horns.

With the uterine horn model, an initial score to represent the overall extent of adhesions is given (0 to 4+). The percentage of a surface of the horn involved in adhesions to various organs are given in the tables below the overall adhesion score.

In the model systems employed in the examples reported herein, the exemplary compound U83,836e was shown to reduce

the incidence of peritoneal adhesions. In these Examples, drug was delivered at a rate of 10 μl/hour. The concentration ranges employed were 0.06-0.6 mg/ml. For purposes of preventing adhesion formation in accordance with the present invention, it is not believed that high systemic levels of lazaroid compounds would be necessary.

Example 1

The efficacy of lazaroid U83,836e in preventing adhesion formation was evaluated in the sidewall model. The drug was delivered for 7 days at a rate of 10 μl/hr and the animals were sacrificed after 7 days. The vehicle was 0.02 mg/ml citric acid, 0.0032 M sodium citrate, and 0.077 M NaCl, pH 3.5. Relative to the control, U83,836e was found to be efficacious in adhesion reduction. The results are summarized in Table 1. A student t test analysis of the data was performed and the results are reported in Table 1 as well.

TABLE 1

Treatment	% Adhesions	Adhesion Score
Vehicle Control	50%	2+[A]
	80%	2+[A]
	80%	2+
	100%	2+
	100%	3+
	90%	3+
Mean:	83.3% ± 17	
0.6 mg/ml Lazaroid	0%	0+
	0%	0+
	0%	0+
	0%	0+
	20%	1+
	40%	1+
Mean[C]:	10.0% ± 15.28	
0.06 mg/ml Lazaroid	0%	0+[B]
	0%	0+
	30%	1+
	70%	1+
	0%	0+
	80%	1+
Mean[D]:	30.0% + 33.17	

A: inflammation
B: bleeding, inflammation at sidewall
C: p = 0.000
D: p = 0.006

Example 2

Lazaroid U83,836e was examined in the double uterine horn model for adhesion prevention. The drug was delivered for 7 days at a rate of 10 µl/hour and the animals were sacrificed at day 7. The statistical analysis done on the data from the double uterine horn model (nonparametric data) is done on the overall score. The data is rank ordered, a rank value given and an analysis of variance on the ranks is performed. The results are summarized in Tables 2 and 3.

TABLE 2

Treatment	Overall Adhesion Score
Vehicle Control	3.5+
	2.5+
	3+
	3+
	3.5+
	3+
0.6 mg/ml Lazaroid	1+
	1.5+
	1.5+
	1.5+
	1+
	1.5+
0.06 mg/ml Lazaroid	1.5+
	2.5+
	0.5+
	1.5+
	0.5+
	1.5+

TABLE 3
% Organ Involvement in Uterine Horn Adhesion

Treatment	Right Horn				Left Horn			
	Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right
Control	40	60	40	60	40	60	40	60[b]
	40	30	20	0	40	30	10	0[a]
	30	80	50	50	30	80	50	50[b]
	40	80	0	30	40	80	0	30
	30	100	40	40	30	100	40	40[b]
	20	70	10	10	20	70	30	10[b]
Mean	33.3	70	26.7	31.7	33.3	70	28.3	31.7
0.6 mg/ml Lazaroid	0	0	10	0	0	10	0	0[a]
	0	0	10	10	0	0	10	10
	0	20	0	0	0	20	20	0
	0	0	30	20	0	0	30	20
	10	0	20	0	10	0	10	0
	0	10	0	0	0	10	20	0
Mean	1.7	5	11.7	5	1.7	6.7	15	5
0.06 mg/ml Lazaroid	0	20	30	0	0	20	10	0
	20	30	10	40	20	30	10	40[a]
	0	0	10	0	0	0	10	0
	0	20	10	30	0	0	0	30
	0	0	0	0	0	10	0	0
	0	10	20	20	0	10	20	20
Mean	3.3	13.3	13.3	15	3.3	11.7	8.3	15

a. Bladder, horn or bowel adhered to the sidewall (at either tube or tube suture)
b. Horn and bowel or bladder to sidewall

Statistical analysis was performed on the overall score of the nonparametric data taken from Table 2. The data was rank ordered and assigned a rank value. Analysis of the variance of the ranks was then performed and the resulting student t test results are summarized below.

Treatment	Rank order	p value
Control	15.4 + 1.72	---
0.6 mg/ml lazaroid	6.5 + 2.12	0.000
0.06 mg/ml lazaroid	6.58 + 3.93	0.000

Example 3

The efficacy of lazaroid U83,836e in the double uterine horn model was further evaluated in a kinetics study. In this study, the pump was disconnected at various times after surgery to determine the time period of exposure to the drug effective to reduce adhesion formation. The efficacy of the lazaroid in preventing adhesions improved at longer exposure times (72 hours) for the two concentrations tested. The results are summarized in Tables 4 and 5.

TABLE 4

Treatment	Overall Adhesion Score
Vehicle Control	3.5+
	2.5+
	3.5+
	3.5+
	3.5+
	2.5+
0.6 mg/ml Lazaroid 24 hour D/C	3+
	1+
	2+
	2+
	1.5+
	1.5+
0.6 mg/ml Lazaroid 48 hour D/C	2.5+
	1.5+
	1.5+
	2+
	1.5+
	2+
0.6 mg/ml Lazaroid 72 hour D/C	1+
	1+
	1+
	1.5+

Treatment	Overall Adhesion Score
	1+
	1+
0.06 mg/ml Lazaroid 24 hour D/C	2.5+
	Died
	1+
	2.5+
	1+
	3+
0.06 mg/ml Lazaroid 48 hr D/C	1+
	1+
	1.5+
	1+
	2.5+
	1+
0.06 mg/ml Lazaroid 72 hour D/C	1.5+
	1+
	1+
	1+
	0.5+
	1+

TABLE 5
% Organ Involvement in Uterine Horn Adhesion

Treatment	Right Horn				Left Horn			
	Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right
Control	40	70	30	50	40	70	30	50**
	40	0	30	60	40	0	30	60*
	60	30	40	70	60	30	60	70
	80	60	50	40	80	60	30	40
	40	100	40	50	40	100	40	50**
	20	40	30	0	20	40	30	0*
Mean	46.7	50	36.7	45	46.7	50	36.7	45
0.6 mg/ml Lazaroid 24 hr D/C	100	30	40	0	100	30	30	0*
	10	0	10	10	10	0	0	10*
	30	0	50	0	30	0	10	0
	0	0	40	20	0	0	20	20**
	10	40	30	0	10	40	0	0*
	0	20	10	10	0	20	10	10**
Mean	25	15	30	6.7	25	15	11.7	6.7
0.6 mg/ml Lazaroid 48 hr D/C	40	30	20	0	40	30	30	0
	0	20	30	0	0	20	0	0*
	0	20	40	0	0	0	0	0*
	0	10	50	10	0	10	20	10**
	0	10	30	20	0	10	20	20
	0	40	30	10	0	40	10	10**
Mean	6.7	21.7	33.3	6.7	6.7	18.3	13.3	6.7
0.6 mg/ml Lazaroid 72 hr D/C	0	10	0	0	0	10	30	0
	0	0	20	20	0	0	20	20

Treatment	Right Horn				Left Horn			
	Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right
	0	0	20	10	0	0	10	10*
	10	0	20	10	10	0	10	10
	0	0	20	30	0	0	20	30
	0	0	30	0	0	0	10	0
Mean	1.7	1.7	18.3	11.7	1.7	1.7	16.7	11.7
0.06 mg/ml Lazaroid 24 hr D/C	50	0	30	10	40	0	10	10*
	DIED D3 P/O							
	20	0	30	10	10	0	10	10*
	10	40	40	20	10	40	30	20**
	0	10	40	0	0	10	0	0
	50	10	30	30	50	10	40	30
Mean	26	12	34	14	22	12	18	14
0.06 mg/ml Lazaroid 48 hr D/C	0	20	20	0	0	20	0	0
	0	20	10	0	0	20	0	0
	0	30	40	0	0	10	10	0
	10	0	0	0	10	0	10	0
	20	20	30	0	20	20	10	0**
	0	10	20	0	0	10	10	0
Mean	5	16.7	20	0	5	13.3	6.7	0
0.06 mg/ml Lazaroid 72 hr D/C	10	10	10	0	10	10	30	0*
	0	10	0	0	0	10	20	0*
	0	0	30	0	0	0	10	0
	0	20	0	0	0	20	10	0
	0	0	10	0	0	0	10	0
	10	0	0	0	10	0	30	0*
Mean	3.3	6.7	8.3	0	3.3	6.7	18.3	0

* Bladder, horn or bowel adhered to the sidewall (at either tube or tube suture)
** Horn and bowel or bladder to sidewall.

Statistical analysis was performed on the overall score of the nonparametric data taken from Table 4 The data was rank ordered and assigned a rank value. Analysis of the variance of the ranks was then performed and the resulting student t test results are summarized below.

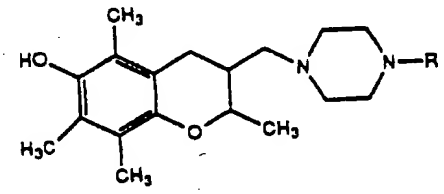
Test System	Time	Rank Score	p value
Control	---	37.2 + 3.3	---
0.6 mg/ml lazaroid	24	24.0 + 8.2	0.004
	48	25.3 + 4.2	0.000
	72	11.5 + 4.5	0.000
0.06 mg/ml lazaroid	24	24.1 + 12.01	0.03
	48	15.3 + 8.83	0.000
	72	10.1 + 5.98	0.000

While there have been shown and described the fundamental novel features of the invention, it will be understood that various omissions, substitutions and changes in the form and details illustrated may be made by those skilled in the art without departing from the spirit of the invention. It is the intention, therefore, to be limited only as indicated by the scope of the following claims.

WHAT IS CLAIMED IS:

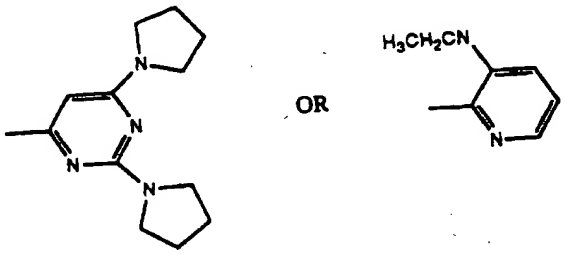
1. A method for prevention of formation of adhesions between organ surfaces, comprising administering an effective amount of at least one lazaroid for a period of time sufficient to permit tissue repair.

2. A method according to claim 1 wherein said lazaroid comprises a compound of general formula I:

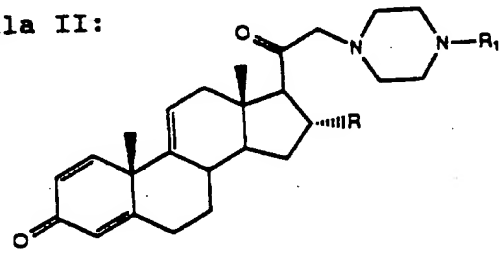


wherein R represents a formula:

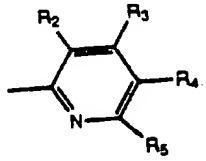
Ia Ib



or formula II:



wherein R represents H or CH_3; R_1 represents formula Ia, as defined above, or formula IIa:



wherein R_2, R_3, R_4, and R_5 independently represent H or NR_6R_7 wherein R_6 and R_7 independently represent H and C_1-C_6 alkyl.

3. A method according to claim 2, wherein the lazaroid comprises: 2-[[4-(2,6-Di-1-pyrrolindinyl-4-pyrimidinyl)-1-piperazinyl] methyl]-3,4-dihydro-2,5,7,8-tetramethyl-2H-1-benzopyran-6-ol, dihydrochloride;(-)-2-[[4-(2,6-Di-1-pyrrolindinyl-4-pyrimidinyl)-1-piperazinyl] methyl]-3,4-dihydro-2,5,7,8-tetramethyl-2H-1-benzopyran-6-ol, 2-hydroxy-1,2,3-propanetricarboxylate; 2H-1-benzopyran-6-ol,2-[[4-[3-(ethylamino)-2-pyridinyl]-1-piperazinyl]methyl]-3,4-dihydro-2,5,7,8-tetramethyl-, hydrochloride;2H-1-benzopyran-6-ol,2-[[4-[3-(ethylamino)-2-pyridinyl]-1-piperazinyl]methyl]-3,4-dihydro-2,5,7,8-tetramethyl-, (Z)-2-butenedioate; 21-[4-[5,6-bis(diethylamino)-2-pyridinyl]-1-piperazinyl]-16-alpha-methyl-pregna-1,4,9(11)-triene-3,20-dione, hydrochloride; 21-[4-[3-ethylamino)-2-pyridinyl]-1-piperazinyl-16-alpha-methyl-pregna-1,4,9(11)-trien-3,20-dione, -(Z)-2-butenedioate; 21-[4-[3-ethylamino)-2-pyridinyl]-1-piperazinyl-16-alpha-methyl-pregna-1,4,9(11)-trien-3,20-dione, hydrochloride; 21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16-alpha-methyl)-pregna-1,4,9(11)-triene-3,20-dione monomethanesulfonate; 21-(4-(2,6-di-1-pyrrolindinyl-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione, (Z)-2-butenedioate; 21-(4-(2,6-di-1-pyrrolindinyl-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione, monomethanesulfonate; 16-alpha-methyl-21-[4-[4,6-bis(2-pyridinyl)-1,3,5-triazin-2-yl]-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione, monomethanesulfonate; or 16-alpha-methyl-21-[4-[2,6-bis(2-

pyridinyl)-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione, monomethanesulfonate.

4. A method according to claim 1, wherein said lazaroid comprises 2-[(2,6-di-1-pyrrolidinyl)-4-pyrimidinyl-methylaminoethanol or 4-[3-(ethylamino)-2-pyridinyl] piperazine and salts thereof.

5. A method according to claim 1, wherein said tissue repair comprises re-epithelization.

6. A method according to claim 1, wherein said tissue repair comprises mesothelial repair.

7. A method according to claim 1, wherein the lazaroid is administered in conjunction with a delivery vehicle which maintains an effective local concentration at the injury site of said lazaroid compound.

8. A method according to claim 7, wherein said effective local concentration ranges between about 0.007ng and about 0.033 mg/hr/cm^2.

9. A method according to claim 8, wherein said effective local concentration ranges between about 0.007μg and about 6.7 μg/hr/cm^2.

10. A method according to claim 7, wherein said effective local concentration ranges between about 0.04 ng and about 0.2 mg/hr/kg.

11. A method according to claim 10, wherein said effective local concentration ranges between about 0.04 μg and about 40 μg/hr/kg.

12. A method according to claim 1, wherein the lazaroid compound is administered in the form of microcapsules or microspheres.

13. A method according to claim 12, wherein the microcapsules or microspheres comprise a biodegradable polymer selected from the group consisting of poly(dl-lactides), poly(dl-lactide-co-glycolides), polycaprolactones, polyglycolides, polylactic acid-co-glycolides, poly(hydroxybutyric acids), polyortho-esters, polyacetals and mixtures thereof.

14. A method according to claim 1, wherein the lazaroid compound is administered in a form of a film.

15. A method according to claim 14, wherein the film comprises a biodegradable polymer selected from the group consisting of poly(dl-lactides), poly(dl-lactide-co-glycolides), polycaprolactones, polyglycolides, polylactic acid-co-glycolides, poly(hydroxybutyric acids), polyortho-esters, polyacetals and mixtures thereof.

16. A method according to claim 1, wherein the lazaroid compound is administered in the form of liposomes.

17. A method according to claim 16, wherein the liposomes comprise L-alpha-distearoyl phosphatidylcholine.

18. A method according to claim 1, wherein the lazaroid compound is administered in the form of a lipid foam.

19. A method according to claim 1, wherein the lazaroid compound is administered in the form of an instillate.

20. A method according to claim 19, wherein the instillate comprises a high-molecular-weight carrier selected from the group consisting of dextrans, cyclodextrans, hydrogels, carboxymethylcellulose, hyaluronic acid, chondroitin sulfate and mixtures thereof.

21. A method according to claim 1, wherein the lazaroid compound is administered in combination with an absorbable mechanical barrier.

22. A method according to claim 21, wherein the absorbable mechanical barrier comprises oxidized regenerated cellulose.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/14938

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,87 01706 (UPJOHN CO) 26 March 1987 cited in the application see the whole document ---	1-23
A	WO,A,91 19482 (INSITE VISION INC) 26 December 1991 cited in the application see the whole document -----	1-23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 1996	02.04.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Mair, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/14938

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although all claims are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition (Rule 39.1 (iv) PCT).

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/14938

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8701706	26-03-87	EP-A-	0263213	13-04-88
		AT-T-	130307	15-12-95
		AU-B-	614661	05-09-91
		AU-B-	4080689	07-12-89
		AU-B-	593284	08-02-90
		AU-B-	6335686	07-04-87
		CA-A-	1308707	13-10-92
		CN-B-	1030319	22-11-95
		DE-D-	3650440	21-12-95
		EP-A-	0238545	30-09-87
		FI-B-	94417	31-05-95
		JP-A-	5112597	07-05-93
		JP-B-	5035158	25-05-93
		JP-T-	63500868	31-03-88
		NO-B-	176762	13-02-95
		US-A-	5099019	24-03-92
		US-A-	5322943	21-06-94
		US-A-	5175281	29-12-92
		US-E-	RE35053	10-10-95
		US-A-	5268477	07-12-93
		US-A-	5380839	10-01-95
		US-A-	5380840	10-01-95
		US-A-	5382661	17-01-95
		US-A-	5380841	10-01-95
WO-A-9119482	26-12-91	US-A-	5124154	23-06-92
		AU-B-	8090791	07-01-92
		CA-A-	2085245	13-12-91
		EP-A-	0660717	05-07-95
		US-A-	5252319	12-10-93
		US-A-	5256408	26-10-93
		US-A-	5209926	11-05-93
		US-A-	5332582	26-07-94